A PHASE 1, NON-RANDOMIZED, OPEN-LABEL, PARALLEL-GROUP SINGLE-DOSE STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF INTRAVENOUS RIVIPANSEL (PF-06460031) IN SUBJECTS WITH MODERATE HEPATIC IMPAIRMENT AND IN HEALTHY SUBJECTS WITH NORMAL HEPATIC FUNCTION

Investigational Product Number:	PF-06460031
Investigational Product Name:	Rivipansel
United States (US) Investigational New Drug (IND) Number:	77,984
European Clinical Trials Database (EudraCT) Number:	Not Applicable
Protocol Number:	B5201006
Phase:	1

[redacted]

[redacted]

Document History

Document	Version Date	Summary of Changes
Original protocol	27 June 2016	Not Applicable (N/A)

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Identifier	**Screening**[a]	**Day 0**	**Day 1**										**Day 2**	**Day 3**	**Day 4**	**Day 5**	**28-day Follow-up Phone Call**
Hours Relative to Dosing			**0**	**0.33**	**1**	**3**	**4**	**6**	**8**	**10**	**12**	**16**	**24**	**48**	**72**	**96**	
Informed consent	X																
Inclusion/exclusion criteria	X	X															
CRU confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Medical history	X	X[b]															
Medication history	X	X															
Physical examination[c]	X	X														X	
Demography	X																
Height[d] and Weight	X																
Alcohol Test[e]	X	X															
Child-Pugh Classification[f]	X[h]	X															
Ascites evaluation[f]	X[h]	X															
Encephalopathy Grade evaluation[f,g]	X[h]	X															
Serologic tests: HIV-1 antibody, HBsAg and HCV antibody	X																
Safety laboratory tests[i]	X	X														X	
Reproductive status	X																
Contraception check	X															X	
Serum FSH[j]	X																
Urine drug test	X	X															
Supine 12-lead electrocardiogram (ECG)	X		X[k]													X	
Single supine blood pressure/pulse rate and temperature	X		X[k]		X[m]		X[l,m]		X[l,m]				X			X	
Study medication administration after fasting for at least 4 hours			X														
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X[p]
Insertion of intravenous catheter[n]			X[k]														
Standardized meals		X			X		X			X			X	X	X	X	
Concomitant treatment(s)			X	→	→	→	→	→	→	→	→	→	→	→	→	X	
Blood sample for determination of rivipansel unbound fraction[o]					X												

Visit Identifier	Screening[a]	Day 0	Day 1										Day 2	Day 3	Day 4	Day 5	28-day Follow-up Phone Call
Hours Relative to Dosing			**0**	**0.33**	**1**	**3**	**4**	**6**	**8**	**10**	**12**	**16**	**24**	**48**	**72**	**96**	
Discharge from CRU																X	

Abbreviations: → = ongoing/continuous event; CRU = clinical research unit; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; INR = international normalized ratio; PT = prothrombin time

a. Subject will be screened within 28 days prior to administration of study medication. For hepatic impairment subjects, see footnote f.

b. On Day 0, review changes in medical history since screening visit.

c. Full physical examination at screening and on Day 5, limited physical examination on Day 0.

d. Height measurement only at screening when full physical examination is performed.

e. Breath or blood alcohol test (method based on discretion of the investigator) for hepatic impairment subjects. For healthy subjects, the alcohol test can be done at the discretion of the investigator.

f. Hepatic impairment subjects only: Child-Pugh classification, encephalopathy grade and ascites evaluations to be performed within the 14 days prior to administration of study medication.

g. Encephalopathy grade evaluation includes number connection test and blood ammonia level (Described in Appendix 1).

h. Second screening visit to be performed for hepatic impairment subjects if a subject is not able to provide documentation of stable hepatic disease (ie, copy of recent lab tests, in addition to medical chart) within the last 30 days (no worsening clinical signs of hepatic impairment, or no worsening of total bilirubin or prothrombin time by more than 50%). See Screening section for details.

i. Includes chemistry, hematology (including PT/INR) and urinalysis, and after fasting for at least 4 hours.

j. To be conducted for females who have achieved postmenopausal status, defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause.

k. Pre-dose.

l. The Day 1 Hour 4 and Hour 8 vital signs will be collected on the source document only.

m. Temperature does not need to be collected at this timepoint.

n. Insertion of the intravenous catheter for collection of blood samples is optional.

o. Sample will be analyzed only if a pharmacokinetic difference in subject groups is observed.

p. Each subject will have a follow up phone call no earlier than 28 days and no later than 31 days after study drug administration to assess for adverse events (AEs) and serious adverse events (SAEs).

Pharmacokinetic Sampling Schema

Visit Identifier	**1**										**2**		**3**	**4**	**5**
Hours After Dose	**0**	**0.33**	**1**	**3**	**4**	**6**	**8**	**10**	**12**	**16**	**24**	**36**	**48**	**72**	**96**
Study treatment administration	X														
Pharmacokinetic blood sampling	X[a]	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Pre-dose sample collection.

b. Timing of sample collection based on stop time of infusion of study medication.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Rivipansel is being developed as a pan-selectin antagonist for the treatment of vaso-occlusive crisis (VOC) in subjects with Sickle Cell Disease (SCD) and a Phase 3 study is ongoing.

1.2. Background

SCD is one of the most prevalent genetic disorders in the United States (US), affecting approximately 100,000 people.[1] It is a chronic condition with substantial morbidity and mortality, and is responsible for more than 75,000 hospitalizations per year in the US with an average in-patient stay of 6.1 days.[2] Both children and adults are affected, and greater mortality is seen in those with more severe disease.

SCD refers to a group of autosomal recessive inherited disorders of the hemoglobin β-globin gene in which a single nucleotide substitution results in the presence of valine instead of glutamic acid in the β-globin chain and leads to the presence of Hemoglobin S (Hb S). Hb S tends to polymerize when deoxygenated, this being the primary indispensable event in the molecular pathogenesis of SCD.[3] Individuals homozygous for Hb S have sickle cell anemia (SCD-SS). Those who are compound (double) heterozygotes have 1 copy of the gene for Hb S and 1 copy of the gene for either Hb C (SCD-SC), Hb β^+-thalassemia (SCD-Sβ^+-thal), or Hb β^0-thalassemia (SCD-Sβ^0-thal).[4]

SCD is associated with a number of serious and potentially disabling conditions that manifest similar symptoms although there may be variation in severity by genotype. Most notable is the VOC, an extremely painful and serious consequence of SCD, resulting from acute ischemic tissue injury.

Over the course of a year, about 60% of patients with SCD-SS will have at least 1 severe VOC,[5] which typically presents as an episode of pain and inflammation, at 1 or more sites. VOC episodes occur with varying degrees of severity, and at varying intervals throughout life and, as the clinical hallmark of SCD, are responsible for the vast majority of hospitalizations (>90%). They result in significant morbidity, interruption of daily functioning and mortality. Other problems that occur in patients with SCD include ischemic and hemorrhagic stroke, acute chest syndrome (ACS), splenic sequestration, dactylitis, osteonecrosis, priapism, leg ulcers, and nephropathy.[3,6,7,8] Most SCD-related deaths occur during episodes of acute VOC, and are due to ACS or stroke.[9] Patients can become symptomatic with pain as early as 6 months of age; thus, VOCs are an important cause of morbidity throughout life, resulting in disruption to the individual's psychosocial development, education and employment consequent upon the severe pain and the frequent need for hospitalization. They also potentially contribute to premature death.

Current medical management of SCD includes hydroxyurea, which is used to increase fetal hemoglobin (Hb F) concentration with the aim of reducing the number of VOC's. Treatment of acute VOC includes mainly supportive measures such as opioid analgesics, hydration and supplemental oxygen. There is no mechanism-based treatment currently available, so this remains an unmet medical need. Most patients attempt pain management at home, and seek

medical care only when this fails. Therefore, many painful episodes do not come to medical attention.[10]

The etiology of VOC involves dual mechanisms: a mechanical component, by which the sickled red blood cells (RBCs) become caught in the post-capillary venules, and an associated inflammatory component in which white blood cells (WBCs) adhere to the endothelium. Together, these 2 mechanisms lead to vascular occlusion and tissue ischemia.

Selectins are a family of adhesion molecules involved in trafficking and extravasation of leukocytes.[17] During the inflammatory response, leukocytes extravasate from the bloodstream and migrate to the sites of inflammation where they participate in the defense against pathogens or other inflammatory processes. This recruitment of leukocytes, which begins with the initial recognition and binding of the leukocytes to the endothelial cells that line the walls of the vasculature, is mediated by selectins.[18]

Three selectins are known to bind carbohydrate structures on cells in interactions characterized by fast kinetics that allow cell adhesion to proceed under the shear forces of blood flow.[19] P-selectin is located on platelets and is also pre-formed and stored in Weibel-Palade bodies within the endothelial cells. It is a "first responder" and is expressed at the endothelial cell surface within 30 minutes of an acute inflammatory response.[20] E-selectin is not pre-formed and stored, but requires de novo protein synthesis and is expressed on the endothelium 3 to 5 hours after activation.[21] Both of these selectins are responsible for the early recognition and adhesion of leukocytes to the vascular endothelium. L-selectin is located on a subset of leukocytes and participates in rolling and adhesion and plays a major role in homing to the lymph nodes.[17]

Rivipansel is a pan-selectin antagonist, a compound found to inhibit selectin binding in vitro and to inhibit selectin-mediated effects in vivo. There are no other known approved therapeutic agents in this class.

Pharmacokinetic (PK) data for rivipansel (GMI-1070) are available from 2 studies in healthy volunteers (GMI-1070-101 and GMI-1070-102), and from a third study conducted in patients with SCD 18 to 50 years of age who, at the time of the study, were not experiencing a VOC (GMI-1070-103). All of these studies were undertaken by Glycomimetics (GMI), from whom Pfizer in-licensed rivipansel. Rivipansel doses used in all GMI studies were based on the salt whereas in all Pfizer studies, including the current study, the dose will be based on the active moiety of rivipansel.

In the first study (GMI-1070-101), subjects received single intravenous (IV) doses of rivipansel 2, 5, 10, 20, or 40 mg/kg or placebo over 20 minutes. In the second study (GMI-1070-102), subjects received multiple IV doses of rivipansel 5, 10, or 20 mg/kg or placebo every 8 hours for a total of 13 doses. An additional group of subjects received a loading dose of 40 mg/kg, followed by multiple doses of rivipansel 20 mg/kg every 8 hours for a total of 6 doses. These studies evaluated a total of 72 healthy adult subjects (54 rivipansel, 18 placebo).

Mean values for C_{max} (maximum observed concentration), AUC_{last} (area under the concentration-time curve [AUC] from time 0 to the time of the last quantifiable concentration), and AUC_{inf} (AUC from time 0 to infinity) increased in a dose-proportional manner, providing evidence of linear PK. After a single 20 mg/kg dose, the mean ± standard deviation (SD) C_{max} was 256±43.7 mg/L. The time of peak concentration (T_{max}) corresponded to the time of the end of infusion and the collection of the first blood sample for determination of rivipansel. The volume of distribution was consistent across dose levels, 0.130 to 0.181 L/kg. Clearance was consistent across dose levels (0.211 to 0.284 mL/min/kg) and the mean elimination half-life ($t_{½}$) ranged from 6.67 to 7.41 hours. Urine collection after multiple dose administration showed a minimum of 89% of the dose was recovered intact in the urine, and renal clearance (CL_r) was less than filtration clearance, consistent with tubular reabsorption.

The third study (GMI-1070-103) was an open-label study of IV rivipansel in 15 adult subjects with stable SCD who received a loading dose of IV rivipansel 20 mg/kg over 20 minutes, followed 10 hours later by a dose of IV rivipansel 10 mg/kg over 20 minutes. The PK was observed to be consistent with that in the healthy volunteers.

In these 3 studies, there were no clinically significant electrocardiogram (ECG) or physical examination findings. With 1 exception, all adverse events (AE) in subjects receiving rivipansel were Grade 1 or 2. Severe symptomatic anemia (Grade 4) that occurred in 1 subject with stable SCD was considered to be remotely related to the study medication, and resolved with therapy. No serious adverse events (SAE) were reported in these studies.

B5201001, a thorough QT (time from ECG Q wave to the end of the T wave) study in 48 healthy African-American subjects who received a single dose of rivipansel 4 g active over 20 minutes, showed a lack of QTc (QT corrected for heart rate) effect. There were no SAEs, no AE's with clinical sequelae and no deaths due to AEs. No new Adverse Drug Reactions (ADRs) for rivipansel were identified in the study but 1 subject discontinued the study due to an AE of "alanine aminotransferase (ALT) increased" following treatment with rivipansel.

A randomized, placebo-controlled Phase 2 trial (GMI-1070-201), evaluating the efficacy, safety, and PK of multiple IV doses of rivipansel in 76 subjects 12 to 60 years of age who were hospitalized for sickle cell VOC has also been undertaken. This study included two dosing schedules; the first cohort received 20 mg/kg loading dose, then 10 mg/kg every 12 hours (q12 h) until 7 days, (maximum 15 doses) and the second cohort received 40 mg/kg loading dose, then 20 mg/kg q12 h until 7 days, (maximum 15 doses). Each IV dose was administered over 20 minutes. There were no clinically significant ECG or clinical findings associated with cardiac toxicity in these subjects. Total treatment-emergent adverse event (TEAE) rates were comparable across groups. SAE's and those SAEs considered "related to treatment" were also comparable across groups. Eleven (11, 14.4%) subjects discontinued study drug due to AEs (8 subjects in the active group, and 3 subjects in the placebo group). No subjects discontinued the study due to AEs. A total of 28 SAEs were reported, encompassing 29 events across 23 subjects. A 30% SAE rate was seen in both active and

placebo groups. The most common SAE was re-hospitalization for VOC. No subjects died during the study.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator Brochure (IB).

1.3. Rationale

1.3.1. Study Rationale

Sickle cell disease can cause progressive injury to the liver with fibrosis and decreased liver function by adulthood.[22] Although rivipansel is known to be primarily eliminated by the kidney (>90% of dose excreted in urine based on data from the Single Ascending Dose study GMI-1070-101), hepatic function can have an effect on the PK of drugs for which the excretion is primarily renal. This study is therefore being conducted to evaluate the effect of hepatic impairment on the PK, safety and tolerability of rivipansel. Results from this study will be used in conjunction with collective safety, efficacy, and PK/pharmacodynamic (PD) data from other rivipansel studies to provide recommendations on dosing for subjects with hepatic impairment.

1.3.2. Dose Rationale

A single 840 mg dose of IV rivipansel will be used in this study as it is the dose selected for maintenance dosing in the rivipansel Phase 3 program. IV doses of rivipansel as high as 4 g (as a single dose) have been well tolerated in healthy volunteers. In the Phase 2 study multiple doses, using a loading dose of 40 mg/kg followed by doses of 20 mg/kg given every 12 hours for up to 7 days were also well tolerated. Therefore, it is expected that potential increases in exposure due to hepatic impairment with a single dose of 840 mg should not pose a safety concern. Single-dose administration was chosen because time-independent PK of rivipansel have been demonstrated at the anticipated concentrations, and thus single-dose PK will be able to adequately predict multiple-dose PK.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objectives:	**Primary Endpoints:**
• To evaluate the effect of moderate hepatic impairment on the PK of rivipansel following a single 840 mg IV dose. • To evaluate the safety and tolerability of a single 840 mg IV dose of rivipansel in subjects with moderate hepatic impairment and in healthy subjects with normal hepatic function.	• Primary: AUC_{inf} (or AUC_{last}, as data permit), CL. • Safety will be assessed by physical examinations, AE monitoring, 12-lead ECGs, supine blood pressure (BP) and pulse rate, and safety laboratory tests.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the effect of moderate hepatic impairment on additional PK parameters for rivipansel following a single 840 mg IV dose.	• Secondary: AUC_{last}, C_{max}, $t_{½}$, V_{ss}.

3. STUDY DESIGN

3.1. Study Overview

This study is a Phase 1 open-label, single-dose, single-treatment, non-randomized study of rivipansel in subjects with moderate hepatic impairment and healthy subjects with normal hepatic function. Since rivipansel is primarily eliminated renally, a reduced study design with two groups (control subjects and subjects with moderate hepatic impairment) was considered adequate to characterize the PK in subjects with hepatic impairment.

The Child-Pugh Score will be utilized to assess entry criteria and to assign subjects to the appropriate hepatic-impairment group. Child-Pugh assessments will be performed within the 14 days prior to study medication administration and Day 0 (baseline). Subjects should satisfy the criteria for Child-Pugh classification as Moderate Hepatic Impairment (Class B Score 7-9) for both assessments in order to be enrolled into the study. The subjects' hepatic function will be ranked based on clinical signs and liver function test results (Table 1).

Table 1. Assessment of Hepatic Impairment: Child-Pugh Score

Assessment Parameters	Assigned Score for Observed Findings		
	1 point	2 points	3 points
Encephalopathy Grade[a]	0	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum Bilirubin (mg/dL)	<2	2 to 3	>3
Serum Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Prothrombin Time (seconds prolonged)	<4	4 to 6	>6
Classification of clinical severity: Mild (Class A): Total score 5-6 points Moderate (Class B): Total score 7-9 points Severe (Class C): Total score >9 points			

a. Grade 0: Normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps (cycles per sec) waves.
Grade 2: Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
Grade 3: Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slow waves.
Grade 4: Unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity.
See Appendix 1 for details.

A total of approximately 16 subjects will be enrolled; 8 subjects with moderate hepatic impairment and 8 healthy subjects with normal hepatic function. Healthy subjects with normal hepatic function will be enrolled after all of the subjects with moderate hepatic impairment have completed the in-patient portion of the study and will be matched for age, weight, and gender to the mean demographics of subjects in the moderate hepatic impairment group. Healthy subjects with normal hepatic function will be enrolled to enable comparison of PK parameters between healthy subjects and subjects with moderate hepatic impairment.

Reasonable efforts will be made to enroll an adequate number of subjects (1 to 3 subjects) with Child-Pugh scores of 8 or 9 (based on assessment on Day 0) to ensure that the entire range of moderate hepatic impairment is represented.

Subjects who withdraw from the normal hepatic function or moderate hepatic impairment groups for non-safety related reasons and who are considered to be non-evaluable with respect to the primary PK objective will be replaced at the discretion of the investigator and sponsor such that the number of completed subjects in each group equals eight.

Screening will occur within the 28 days prior to administration of study medication. All subjects will provide informed consent and undergo Screening evaluations to determine their eligibility.

Eligible subjects will be admitted to the Clinical Research Unit (CRU) on Day 0 and will be confined in the CRU until Day 5. On Day 1, subjects will receive a single 840 mg IV dose of rivipansel. Serial blood samples will be collected at specified intervals for 96 hours post-dose for PK assessments, prior to discharge from the CRU on Day 5.

Age/Weight/Gender Matching Criteria:

Subjects with Child-Pugh Class B (moderate) hepatic impairment will be enrolled first and their demographics will be pooled. Enrollment of age-, weight-, and gender-matched healthy subjects with normal hepatic function will begin after all of the moderate hepatic impairment subjects have completed the in-patient portion of the study. Demographics of the healthy subjects will be matched to the pooled demographics of the moderate impairment group such that the body weight of each healthy subject is within ±15 kg of the mean body weight of the subjects with hepatic impairment, age is within ±10 years of the mean age of the subjects with hepatic impairment and the gender ratio for the group is similar (±2 subjects per gender) to the subjects with hepatic impairment. In general, care should be taken when recruiting the healthy subjects such that the entire group is as closely matched as possible in age and body weight to the subjects with hepatic impairment.

Safety assessments (as specified in the Schedule of Activities) will be performed during screening, prior to dosing on Day 1 and post dosing. The total participation time (ie, CRU confinement time for study procedures) for each subject in this study will be approximately 5 nights/6 days (excluding screening). Subjects will have a follow-up phone call no earlier than 28 days and no later than 31 days after study drug administration, to assess for AEs/SAEs.

All procedures and their timelines follow the Schedule of Activities.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment in the study:

4.1.1. All Subjects

1. Female subjects of non-childbearing potential or male subjects who, at the time of screening, are between the ages of 18 and 75 years, inclusive.

2. Female subjects of non-childbearing potential must meet at least 1 of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and a serum follicle-stimulating hormone (FSH) level consistent with the post-menopausal state;

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   c. Have medically confirmed ovarian failure.

   All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

3. Body mass index (BMI) of 17.5 to 40 kg/m^2; and a total body weight >50 kg (110 lb).

4. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

5. Willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.1.2. Healthy Subjects with Normal Hepatic Function

1. Healthy, defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including BP and pulse rate measurement, 12-lead ECG and safety laboratory tests.

2. Normal hepatic function with no known or suspected impairment.

3. Demographically comparable to subjects with hepatic impairment:

   - Body weight will be within ±15 kg of the mean body weight of the pooled group of subjects with moderate hepatic impairment.

   - Age will be within ±10 years of the mean age of the pooled group of subjects with moderate hepatic impairment.

- The gender ratio for the group will be similar (±2 subjects per gender) to the pooled group of subjects with moderate hepatic impairment.

4.1.3. Subjects with Hepatic Impairment

1. Satisfy the criteria for Child-Pugh classification as Moderate Hepatic Impairment (Class B - Score 7-9) within the 14 days prior to administration of study medication and Day 0 (baseline) [Note: As stated in the STUDY DESIGN section, reasonable efforts will be made to enroll an adequate number of subjects (1 to 3 subjects) with Child-Pugh scores of 8 and 9 (based on assessment at Day 0) to ensure that the entire range of moderate hepatic impairment is represented].

2. Hepatic impairment due to primary liver disease and not secondary to other diseases, confirmed and documented by medical history, physical examination, liver biopsy, hepatic ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI).

3. Stable hepatic impairment, defined as no clinically-significant change in disease status within at least the last 30 days, (no worsening clinical signs of hepatic impairment, or no worsening of total bilirubin or prothrombin time by more than 50%) as documented by the subject's recent medical history. If subjects do not have adequate available records, 2 screening visits (Screening and Day 0 visit) will be performed to demonstrate stability of hepatic disease. The 2 visits (if performed) for demonstrating stability of hepatic disease must be at least 7 days apart.

4. On stable doses of medication and/or treatment regimens for at least 4 weeks prior to screening. Such medications would also need to be held stable from screening through study completion. Subjects who are receiving a fluctuating treatment regimen may be considered for inclusion on a case-by-case basis if the underlying disease is under control in the opinion of the investigator and sponsor.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

4.2.1. All Subjects

1. Known hypersensitivity or intolerance to rivipansel.

2. History of febrile illness within 5 days prior to administration of study medication.

3. Any medical or surgical condition that might significantly interfere with the distribution, metabolism, or excretion of rivipansel.

4. A positive urine drug test for illicit drugs. However, subjects with hepatic impairment who test positive for a prescribed medicine can be enrolled.

5. History of abuse of alcohol or binge drinking and/or any other illicit drug use or dependence within 6 months of screening. Binge drinking is defined as a pattern of 5 or more alcoholic drinks (male), or 4 or more alcoholic drinks (female) in about 2 hours. As a general rule, alcohol intake should not exceed 2 drinks per day or 14 drinks per week (1 drink = 5 ounces of wine (150 mL) or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of spirit).

6. Treatment with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the administration of study medication (whichever is longer).

7. Any prior history of malignancy with the exception of:

   - Basal cell carcinoma of the skin; or
   - Squamous cell carcinoma of the skin that has been recurrence-free for ≥5 years; or
   - Other malignancies (regardless of site) that have been recurrence-free for ≥10 years.

8. Pregnant or breastfeeding females; male subjects with partners currently pregnant; fertile male subjects who are unwilling or unable to use a highly effective method of contraception as outlined in the protocol for the duration of the study and for 28 days after the last dose of study medication.

9. Use of herbal supplements within 28 days prior to administration of study medication.

10. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 56 days prior to administration of study medication.

11. History of sensitivity to heparin or heparin-induced thrombocytopenia (if heparin is used to flush intravenous catheters).

12. An estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 based on the four-variable Modification of Diet in Renal Disease (MDRD) equation.

13. Subjects who are unwilling or unable to comply with the criteria in the Lifestyle Requirements section of this protocol.

14. Subjects who are investigator site staff members directly involved in the conduct of the study (including their family members), site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees (including their family members), directly involved in the conduct of the study.

15. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4.2.2. Healthy Subjects with Normal Hepatic Function

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Screening supine 12-lead ECG demonstrating QTcF (QTc using Fridericia's formula) >450 msec or a QRS interval >120 msec at screening. If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTcF or QRS values should be used to determine the subject's eligibility.

3. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), on a single measurement following at least 5 minutes of rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the subject's eligibility.

4. History of alcohol abuse with a positive alcohol test at screening or on Day 0 at the discretion of the investigator.

5. Subjects with **ANY** of the following abnormalities in safety laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

   - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level > upper limit of normal (ULN);

   - Total bilirubin level > ULN.

6. Use of prescription drugs, vitamins, or dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to administration of study medication. As an exception, acetaminophen may be used at doses of ≤1 g/day. Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

7. Positive serologic findings for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg) and /or hepatitis C virus (HCV) antibodies.

4.2.3. Subjects with Hepatic Impairment

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Hepatic carcinoma or hepatorenal syndrome or life expectancy less than 1 year.

3. Prior portal-caval shunt surgery. A subject with a transjugular intrahepatic portosystemic shunt (TIPS) is not excluded provided they meet the Child-Pugh criteria.

4. A positive alcohol test at screening or Day 0 (past history of alcohol abuse is permissible providing that the results of alcohol tests are negative at screening and on Day 0).

5. History of gastrointestinal hemorrhage due to esophageal varices or peptic ulcers less than 4 weeks prior to study entry.

6. Any clinically-significant laboratory abnormality except for those parameters influenced by hepatic impairment.

7. Positive serologic findings for human immunodeficiency virus (HIV) antibodies.

8. Subjects with transaminases >5 × upper limit of normal (ULN). Subjects with transaminases >5 × ULN may be considered for inclusion on a case-by-case basis if, in the opinion of the Investigator and Sponsor, these levels will not affect subject safety.

9. Signs of significant hepatic encephalopathy (> Grade II Portal Systemic Encephalopathy score).

10. Severe ascites and/or pleural effusion.

11. Prior kidney, heart or liver transplant.

12. Twelve (12)-lead ECG demonstrating QTcF >470 msec or a QRS interval >120 msec at screening. If QTcF exceeds 470 msec, or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTcF or QRS values should be used to determine the subject's eligibility.

13. Screening supine BP ≥160 mm Hg (systolic) or ≥90 mm Hg (diastolic), on a single measurement following at least 5 minutes of rest. If BP is ≥160 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the subject's eligibility.

4.3. Lifestyle Requirements

The following guidelines are provided:

4.3.1. Meals and Dietary Restrictions

- Subjects must abstain from all food and drink (except water) for at least 4 hours prior to any safety laboratory evaluations and to administration of study medication. Water is permitted until 1 hour prior to study medication administration. Water may be consumed without restriction beginning 1 hour after dosing. Non-caffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices – see below) may be consumed with meals and the evening snack.

- Breakfast will be provided approximately 1 hour after dosing.

- Lunch will be provided approximately 4 hours after dosing.

- Dinner will be provided approximately 9 to 10 hours after dosing.

- An evening snack may be permitted.

- Meals will be provided following the site's normal schedule on non-dosing days.

- Subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the dose of study medication until collection of the final PK blood sample. While in the clinical research unit (CRU), the total daily nutritional composition should be approximately 55% carbohydrate, 30% fat and 15% protein. The daily caloric intake per subject should not exceed approximately 3200 kcal.

4.3.2. Alcohol, Caffeine and Tobacco

- Subjects will abstain from alcohol from 24 hours prior to admission to the CRU until collection of the final PK sample. Healthy subjects with normal hepatic function may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Subjects will abstain from caffeine-containing products from 24 hours prior to the dose of study medication until collection of the final PK sample. Subjects will abstain from the use of tobacco- or nicotine-containing products from 24 hours prior to the dose of study medication until the end of their confinement in the research unit.

4.3.3. Activity

- Subjects will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, and aerobics) for at least 48 hours prior to each blood collection for safety laboratory tests. Walking at a normal pace will be permitted.

4.3.4. Contraception

4.3.4.1. Females - Childbearing Potential

Females of childbearing potential are excluded from participation.

4.3.4.2. Males

All fertile male subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of study medication. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his partner from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal) provided subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post vasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the usual and preferred lifestyle of the subject.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the team SharePoint site.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is rivipansel (PF-06460031).

5.1. Allocation to Treatment

The investigator will assign subject identification numbers sequentially to the subjects as they are screened for the study. This identifying number will be retained throughout the study. All subjects enrolled will receive a single IV dose of rivipansel 840 mg on Day 1.

5.2. Subject Compliance

Investigational product will be administered under the supervision of investigative site personnel.

5.3. Investigational Product Supplies

5.3.1. Dosage Form and Packaging

Rivipansel (as the sodium salt) will be supplied by Pfizer in vials. Vials will contain rivipansel as a 30 mg/mL solution and the concentration of the solution is based on the active moiety. Rivipansel is presented as a sterile, colorless to pale brown solution for single use administration in a 30 mL clear glass vial sealed with a grey stopper and aluminum over-seal for administration by intravenous infusion. The content of the rivipansel vials should be clear, but a fine swirl or haze of particulate matter may be observed on agitation of the solution.

Sterile vials will be packaged individually and supplied for subsequent unit dose preparation according to the Investigational Product Manual (IPM). Vial adapters and syringe filters will be supplied by Pfizer for dose preparation.

5.3.2. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the subject/caregiver by qualified staff. Dispensing is defined as the provision of investigational product, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, subject, or caregiver in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Rivipansel sterile solution for IV infusion will be prepared according to details specified in the IPM. This will include the requirement for the study drug to be filtered through a 0.22 micron syringe filter upon transfer to the syringe that will be used for administration to the subject. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

5.3.3. Administration

Following an overnight fast of at least 4 hours, subjects will receive investigational product at approximately 0800 hours (±2 hours).

Rivipansel will be infused over 20 ±2 minutes using an administration set that includes a 0.2 or 0.22 micron in-line filter. The details of the IV infusion will be described in the IPM. The start and stop time of the infusion will be recorded.

In order to standardize the conditions on PK sampling days, all subjects will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements) during the first 4 hours after dosing.

5.4. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. See the IPM for storage conditions of the product.

Any storage conditions stated in the SRSD (IB for this study) will be superseded by the storage conditions stated on the product label.

Site staff will follow the standard operating procedure (SOP) for temperature and relative humidity monitoring in the CRU pharmacy.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product-label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

5.5. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.5.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.6. Concomitant Treatment(s)

Healthy subjects with normal hepatic function will abstain from all concomitant treatments, except for the treatment of AEs, as described in the Healthy Subjects with Normal Hepatic Function section of this protocol. Use of prescription drugs, vitamins, or dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to administration of study medication is not allowed. As an exception, acetaminophen may be used at doses of ≤1 g/day. Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

For subjects with impaired hepatic function, treatments intended for other indications should be administered as usual (Subjects with Hepatic Impairment).

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration.

Treatments taken within 28 days before the dose of investigational product will be documented as prior treatments. Treatments taken after the dose of investigational product will be documented as concomitant treatments.

6. STUDY PROCEDURES

6.1. Screening

Subjects will be screened within 28 days prior to administration of investigational product to confirm that they meet the subject eligibility criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in the Subject Information and Consent section. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then subjects do not require re-screening if the Day 0 laboratory results meet the eligibility criteria.

The following procedures will be completed:

- Obtain written informed consent.
- Confirm and document that the subject meets inclusion and exclusion criteria.
- Collect demography.

- Collect height and weight.
- Obtain medical history, including history of illegal drug, alcohol and tobacco use.
- Obtain complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 28 days prior to the planned first dose.
- Check reproductive status.
- Perform contraception check.
- Obtain single supine BP, pulse rate and temperature.
- Conduct full physical examination.
- Perform supine 12-lead electrocardiogram (ECG).
- Following at least a 4-hour fast, collect blood and urine specimens for the following:
    - Safety laboratory tests;
    - Serologic tests: HIV-1 antibody, HBsAg and HCV antibody;
    - Urine drug test;
    - Serum FSH concentration for any female subject who has been amenorrheic for at least 12 consecutive months with no alternative pathological or physiological cause.
- Obtain breath or blood alcohol test (method based on discretion of the investigator) for hepatic impairment subjects. For healthy subjects, the alcohol test can be done at the discretion of the investigator.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Hepatic impairment subjects only: Perform Child-Pugh classification, encephalopathy and ascites evaluations within the 14 days prior to administration of study medication. Encephalopathy grade evaluation includes number connection test and blood ammonia level. Subjects should satisfy the criteria for Child-Pugh classification as Moderate Hepatic Impairment (Class B - Score 7-9). Perform a second screening visit for hepatic impairment subjects if a subject is not able to provide documentation of stable hepatic disease (ie, copy of recent laboratory tests, in addition to medical chart) within the last 30 days (no worsening clinical signs of hepatic impairment, or no worsening of total bilirubin or prothrombin time by more than 50%).

To prepare for study participation, subjects will be instructed on the information in the Lifestyle Requirements and Concomitant Treatment(s) sections of the protocol.

6.2. Study Period

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

- **ECGs**: obtain prior to vital signs measurements and as close as possible to the scheduled time, but prior to blood specimen collection;
- **BP/pulse rate**: obtain as close as possible to the scheduled time, but prior to blood specimen collection;
- **PK blood specimens**: obtain at the scheduled time;
- **All other procedures**: obtain as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.

When an IV catheter is utilized for blood sample collections, ECGs and vital sign (pulse rate and BP and temperature) assessments should be collected prior to the insertion of the catheter.

6.2.1. Day 0

Subjects will be admitted to the CRU on Day 0. The following procedures will be completed following admission to the CRU:

- Review inclusion and exclusion criteria.
- Review changes in the subject's medical history including medication history since screening.
- Conduct limited physical examination.
- Obtain breath or blood alcohol test (method based on discretion of the investigator) for hepatic impairment subjects. For healthy subjects, the alcohol test can be done at the discretion of the investigator.
- Obtain blood and urine samples for safety laboratory tests after fasting for at least 4 hours. The results must have no clinically significant findings, as judged by the investigator, in order for a subject to be given study medication on Day 1.
- Collect urine for drug testing.

- Hepatic impairment subjects only: Re-perform Child-Pugh classification (considered as baseline score), encephalopathy and ascites evaluations. Encephalopathy grade evaluation includes number connection test and blood ammonia level. Subjects should satisfy the criteria for Child-Pugh classification as Moderate Hepatic Impairment (Class B - Score 7-9).

- Assess baseline symptoms/AEs.

- Provide standardized meals as described in the Lifestyle Requirements section. Subjects will begin fasting at least 4 hours prior to dosing on Day 1.

6.2.2. Day 1

Prior to dosing, the following procedures will be completed:

- Collect supine 12-lead ECG.

- Obtain single supine BP, pulse rate and temperature.

- Insert the IV catheter for collection of blood samples (optional).

- Collect a blood sample for PK analysis.

- Commence concomitant treatment monitoring.

- Assess baseline symptoms/AEs.

- After all pre-dose procedures have been completed and after fasting for at least 4 hours, administer the study medication (see the STUDY TREATMENTS and Administration sections).

After dosing, the following procedures will be completed:

- Collect blood samples for PK analysis of rivipansel 0.33, 1, 3, 4, 6, 8, 10, 12 and 16 hours after dosing.

- Collect blood samples for determination of rivipansel unbound fraction 1 hour after dosing.

- Obtain single supine BP and pulse rate 1, 4 and 8 hours after dosing. Hour 4 and Hour 8 collections will be documented on source document only.

- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a non-leading question such as “How do you feel?”

- Monitor concomitant treatments.

- Provide standardized meals 1, 4, and 10 hours after dosing as described in Lifestyle Requirements section.

6.2.3. Day 2

The following procedures will be completed:

- Collect blood samples for PK analysis 24 and 36 hours after dosing on Day 1.
- Obtain single supine BP, pulse rate and temperature.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Monitor concomitant treatments.
- Provide standardized meal(s).

6.2.4. Day 3

The following procedures will be completed:

- Collect blood samples for PK analysis of rivipansel 48 hours after dosing on Day 1.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Monitor concomitant treatments.
- Provide standardized meal(s).

6.2.5. Day 4

- Collect blood samples for PK analysis of rivipansel 72 hours after dosing on Day 1.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Monitor concomitant treatments.
- Provide standardized meal(s).

6.2.6. Day 5

- Collect blood samples for PK analysis of rivipansel 96 hours after dosing on Day 1.
- Conduct full physical examination.
- Perform contraception check.

- Collect supine 12-lead ECG.
- Obtain single supine BP, pulse rate and temperature.
- Collect blood and urine specimens for safety laboratory tests after a fast of at least 4 hours.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Monitor concomitant treatments.
- Provide standardized meal(s).
- Discharge from CRU confinement.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the CRU until such abnormalities are no longer deemed clinically significant, or it is considered safe for outpatient follow-up. If the subject is unable or unwilling to remain in the CRU and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.3. Follow-up Contact

- Each subject will have a follow-up phone call no earlier than 28 days and no later than 31 days after study medication administration to assess for AEs and SAEs.

6.4. Subject Withdrawal/Early Termination

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given investigator site. The early termination visit applies only to subjects who are randomized and then are prematurely withdrawn from the study.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The investigator or site staff should attempt to contact the subject twice. After 2 attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow-up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved AEs.

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Subjects should be questioned regarding their reason for withdrawal. At the early withdrawal visit, every effort must be made to complete the following assessments:

- Full physical examination, if there is a new or ongoing AE or clinically significant abnormal physical finding from the last visit;
- Supine BP and pulse rate measurements;
- 12-lead ECG measurement;
- Blood and urine specimens for safety laboratory tests after fasting for at least 4 hours;
- Blood sample for PK analysis.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

7. ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Safety

7.1.1. Laboratory Tests

The following safety laboratory tests will be performed at times defined in the STUDY PROCEDURES section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled safety laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

The laboratory tests shown in Table 2 will be performed at the timepoints stated in the Schedule of Activities.

Table 2. Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs) PT/INR	BUN/urea and Creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	FSH[b] Urine drug test[c] Serologic tests: HIV-1 antibody, HBsAg and HCV antibody[d]
	Additional Tests (If required for assessment of potential Hy's law cases)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

a Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b At screening only, in females who are amenorrheic for at least 12 consecutive months to assess childbearing potential.
c At screening and Day 0 only.
d At screening only.

- The minimum requirement for drug testing includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines.

- Subjects may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for subjects to receive study medication.

- Any remaining serum/plasma from samples collected for safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. Upon completion of the study, retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the clinical study report (CSR). Samples to be used for this purpose will be shipped to either a Pfizer approved Biospecimen Banking System (BBS) facility or other designated laboratory and retained for up to 1 year following the completion of the study.

7.1.2. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulations. A full physical examination will include assessment of head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes and gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance and the respiratory and cardiovascular systems, and subject-reported symptoms.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

7.1.3. Blood Pressure and Pulse Rate

BP and pulse rate will be measured at times specified in the STUDY PROCEDURES section of this protocol. Additional collection times, or changes to collection times of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine BP will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Blood pressure should not be taken from the arm with an intravenous infusion. Subjects should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

7.1.4. Temperature

Temperature will be measured orally. No eating, drinking or smoking is allowed for 15 minutes prior to the measurement.

7.1.5. Electrocardiogram

ECGs should be collected at times specified in the STUDY PROCEDURES section of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements. If the QTcF interval is increased by ≥45 msec from the baseline, or an absolute QTcF value is ≥500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2 to 4 minutes apart, to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (ie, ≥45 msec from the baseline, or ≥500 msec), then a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTcF values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or sooner at the discretion of the investigator) or QTcF intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to less than 500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

7.2. Pharmacokinetics

7.2.1. Plasma for Pharmacokinetic Analysis of Rivipansel

During all study periods, blood samples 4.0 mL to provide a minimum of 1.5 mL plasma for PK analysis will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the STUDY PROCEDURES section of the protocol.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, case report form [CRF]/DCT).

- Samples will be centrifuged at approximately 1700 × g for about 10 minutes at 4°C. The plasma will be stored in appropriately labeled screw-capped polypropylene tube at approximately -20°C within 1-hour of collection.

- Samples will be analyzed using a validated analytical method in compliance with Pfizer SOPs.

- The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

- As part of understanding the PK of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the CSR.

7.2.2. Plasma for Unbound Fraction Determination of Rivipansel

On Day 1, a blood sample (10.0 mL to provide a minimum of 5.0 mL plasma) for PK analysis will be collected into appropriately labeled tubes containing K_2EDTA at the time specified in the STUDY PROCEDURES section of the protocol. Sample will be analyzed only if a PK difference in subject groups is observed.

All efforts will be made to obtain the PK sample at the exact nominal time relative to dosing. However, a sample obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF/DCT).

- Samples will be centrifuged at approximately 1700 × g for about 10 minutes at 4°C. The plasma will be stored in appropriately labeled screw-capped polypropylene tube at approximately -20°C within 1-hour of collection.

- Samples will be analyzed using a validated analytical method in compliance with Pfizer SOPs.

- The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

- As part of understanding the PK of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the CSR.

7.3. Blood Volume

The total blood sampling volume for individual subjects in this study is approximately 91 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy (EDP), exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;

- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

  Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);

- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of

normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. .

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.2. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.2.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.2.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.2.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.3. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.3.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

Hepatic impairment subjects will be enrolled based on their Child-Pugh scores at Screening and Day 0.

Eight (8) subjects will be enrolled into each of the two study groups (moderate hepatic impairment and healthy with normal hepatic function).

This is an estimation study. The sample size is based on recommendations from the Food and Drug Administration (FDA) Guidance for Industry "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."[23]

9.2. Pharmacokinetic Analysis

The PK concentration population is defined as all subjects treated with study drug who have at least 1 concentration measurement.

The PK parameter analysis population is defined as all subjects treated with study drug who have at least 1 of the PK parameters of interest.

Analysis of variance (ANOVA) will be used to compare the natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} between normal hepatic function group and the impaired hepatic function group. The geometric least squares mean point estimate and the associated 90% confidence intervals (CIs) for the difference of each comparison will be estimated.

Rivipansel PK parameters AUC_{inf}, C_{max}, AUC_{last}, T_{max}, $t_{½}$, CL V_{ss}will be summarized descriptively by group.

Boxplots of mean, median and individual subject parameters will be made across all the groups for AUC_{inf}, AUC_{last} and C_{max}. Concentrations will be listed and summarized descriptively by PK sampling time and group. Summary profiles (means and medians) of the concentration- time data will be plotted across different groups. Individual subject concentration time profiles will be also presented. For summary statistics and summary plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

9.2.1. Plasma

PK parameters of rivipansel following single dose administration will be derived from the concentration-time profiles as follows:

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal rule
AUC_{inf} [a]	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$ [a]	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression
CL [a]	Total clearance of drug from plasma	$Dose/AUC_{inf}$
V_{ss} [a]	Volume of distribution at steady state	CL * MRT, where MRT is the mean residence time

[a] If data permit

Actual PK sampling times and non-compartmental methods will be used in the derivation of PK parameters.

9.3. Safety Analysis

AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any safety laboratory, ECG, BP, or pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and information from physical and/or neurological examination collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as an AE, if those findings meet the definition of AEs. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.4. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development. Unblinded results will be reviewed by a designated limited number of sponsor colleagues within the study team. Refer to the study Data Blinding Plan and/or SAP for specific details including delineation of study team members who will be involved in these unblinded reviews as well as steps to be instituted ahead of initiation of any unblinded review to ensure study integrity is maintained.

9.5. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct for studies conducted at non-Pfizer investigator sites, to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs/DCTs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory

authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

For studies conducted at non-Pfizer investigator sites, it is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF/DCT should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF/DCT is required and should be completed for each included subject. The completed original CRFs/DCTs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs/DCTs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs/DCTs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs/DCTs are true. Any corrections to entries made in the CRFs/DCTs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs/DCTs must match those charts.

In some cases, the CRF/DCT may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF/DCT, and for which the CRF/DCT will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs/DCTs and hospital records), all original signed informed consent documents, copies of all CRFs/DCTs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guidelines for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in the United States

Last subject last visit (LSLV) is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of rivipansel at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs/DCTs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual patients have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by a principal investigator of the results of the study based on information collected or generated by the principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed

publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multi-center study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. Centers for Disease Control and Prevention Sickle Cell Disease homepage. Available at: http://www.cdc.gov/ncbddd/sicklecell/data.html. Accessed February 12, 2014.

2. Davis H, Roscoe M, Moore J, et al. Cost of hospitalizations associated with sickle cell disease in the US. Public Health Rep. 1997;112:40-3.

3. Stuart MJ, Nagel RL. Sickle-cell disease. Lancet. 2004;364:1343-60.

4. Frenette PS, Atweh GF. Sickle cell disease: old discoveries, new concepts, and future promise. J Clin Invest. 2007;117:850-8.

5. Platt OS, Thorington BD, Brambilla DJ, et al. Pain in sickle cell disease: rates and risk factors. N Engl J Med. 1991;325:11-6.

6. Steinberg MH. Management of sickle cell disease. N Engl J Med. 1999;340:1021-30.

7. American Academy of Pediatrics, Section on Hematology/Oncology and Committee on Genetics. Health supervision for children with sickle cell disease. Pediatrics. 2002;109:526-35.

8. Ballas SK. Pain management of sickle cell disease. Hematol Oncol Clin North Am. 2005;19:785-802.

9. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease -- Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639-44.

10. Smith WR, Penberthy LT, Bovbjerg VE, et al. Daily assessment of pain in adults with sickle cell disease. Ann Intern Med. 2008;148(2):94-101.

11. Bunn HF. Pathogenesis and treatment of sickle cell disease. N Engl J Med. 1997;337:762-9.

12. Okpala I. Leukocyte adhesion and the pathophysiology of sickle cell disease. Curr Opin Hematol. 2006;13:40-4.

13. Blum A, Yeganeh S, Peleg A, et al. Endothelial function in patients with sickle cell anemia during and after sickle cell crises. J Thromb Thrombolysis. 2005;19(2):83-6.

14. Kato GJ, Martyr S, Blackwelder WC, et al. Levels of soluble endothelium-derived adhesion molecules in patients with sickle cell disease are associated with pulmonary hypertension, organ dysfunction, and mortality. Br J Haematol. 2005;130:943-53.

15. Turhan A, Weiss LA, Mohandas N, et al. Primary role for adherent leukocytes in sickle cell vascular occlusion: A new paradigm. Proc Natl Acad Sci. 2002;99:3047-51.

16. Kaul DK, Hebbel RP. Hypoxia/reoxygenation causes inflammatory response in transgenic sickle mice but not in normal mice. J Clin Invest. 2000;106(3):411-20.

17. Tedder TF, Steeber DA, Chen A, et al. The selectins: vascular adhesion molecules. Br J Rheumatol. 1995;34:1101-4.

18. Ebnet K, Vestweber D. Molecular mechanisms that control leukocyte extravasation: The selectins and chemokines. Histochem Cell Biol. 1999;112:1-23.

19. Chen S, Springer TA. Selectin receptor-ligand bonds: Formation limited by shear rate and dissociation governed by the Bell model. Proc Natl Acad Sci. 2001;98:950-5.

20. Blann AD, Nadar SK, Lip GYH. The adhesion molecule P-selectin and cardiovascular disease. Eur Heart J. 2003;24:2166-79.

21. Kansas GS. Selectins and their Ligands: Current concepts and controversies. Blood. 1996;88: 3259-87.

22. Schubert TT. Hepatobiliary system in sickle cell disease. Gastroenterology. 1986;90 :2013-21.

23. Guidance for Industry: Pharmacokinetics in patients with impaired hepatic function - Study design, data analysis, and impact on dosing and labeling. FDA Guidance, March 2011.

Appendix 1. Determination of Encephalopathy for the Calculation of the Child Pugh Score

For the calculation of the portosystemic encephalopathy (PSE) index the parameters are evaluated or determined as follows:

A = Degree of consciousness

According to the given grading of the table (clinical estimation of the investigating physician).

B = Number Connection Test

According to the table

C = Tremor

According to the table

D = Ammonia concentration in venous blood

According to the table normal values: 25-94 μg/dL

The weighting is according to the given formula 3×A+B+C+D, and the index calculated by multiplication by 100 and division by 24 (see below).

In deviation from the PSE index form, however, a maximum of only 24 score can be attained in total (not 25).

The evaluation was then done according to the following grading:

PSE-Index (%)

Normal:

- 0: no encephalopathy

Moderate:

- 1-25: encephalopathy grade I
- 26-50: encephalopathy grade II

Severe:

- 51-75: encephalopathy grade III
- 76-100: encephalopathy grade IV grade severe

Portosystemic Encephalopathy (PSE) Examination

PSE-Index

A Grade of consciousness

0 = no abnormality
1= slight absence, phobia, euphoria, shortened attention
2 = lethargy, chronotaraxis, personality change, strange behavior
3 = somnolence, semistupor
4 = coma

B Number of Connection test

0 = <30 sec
1 = 31-50 sec
2 = 51-80 sec
3 = 81-120 sec
4 = >120 sec

C Tremor (arms and hands, ca 30 sec stretched)

0 = no tremor
1 = rare tremor
2 = occasional tremor, not regularly
3 = frequent tremor
4 = continuous tremor

D Ammonia Concentration in venous blood
0 = ≤10% elevated above ULN
1 = 11 - 60% elevated above ULN
2 = 61 - 86% elevated above ULN
3 = 87 - 123% elevated above ULN
4 = >124% elevated above ULN

PSE-sum = 3×A+B+C+D (max 24 scores)

PSE-Index (%) = (PSE-sum x 100)/24

- 26-50: encephalopathy grade II

Severe:

- 51-75: encephalopathy grade III
- 76-100: encephalopathy grade IV grade severe

Appendix 2. Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AE	adverse event
Abs	absolute
ACS	acute chest syndrome
ADR	Adverse Drug Reaction
ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the curve
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BBS	Biospecimen Banking System
BMI	body mass index
BP	blood pressure
BPM	beats per minute
BUN	blood urea nitrogen
CI	confidence interval
CL/F	apparent oral clearance
CL_r	renal clearance
C_{max}	peak or maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CRU	clinical research unit
CSA	clinical study agreement
CSR	clinical study report
CT	computed tomography
CTA	clinical trial application
DCT	data collection tool
DILI	drug-induced liver injury
EC	ethics committee
ECG	electrocardiogram
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
eGFR	estimated glomerular filtration rate
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

Abbreviation	Term
GGT	gamma-glutamyl transpeptidase
GMI	Glycomimetics
Hb	hemoglobin
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IPM	Investigational Product Manual
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LFT	liver function test
LSLV	last subject last visit
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MRI	magnetic resonance imaging
N/A	not applicable
PCD	primary completion date
PD	pharmacodynamic
PK	pharmacokinetic(s)
PT	prothrombin time
QTc	QT corrected for heart rate
QTcF	QTc using Fridericia's formula
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SCD	Sickle Cell Disease
SD	standard deviation
SOP	standard operating procedure
SRSD	single reference study document
$t_{½}$	terminal half-life
TEAE	treatment-emergent adverse event
TIPS	transjugular intrahepatic portosystemic shunt
T_{max}	time to reach maximum concentration
THC	tetrahydrocannabinol
TBili	total bilirubin

Abbreviation	Term
ULN	upper limit of normal
US	United States
VOC	vaso-occlusive crisis
V_{ss}	volume of distribution at steady state
WBC	white blood cell